

1 olanzapine, up to 20 milligrams per day, if
2 they felt it was clinically necessary.

3 The exciting part about Study KB is
4 that it's truly a long-term study in which
5 patients will be monitored for many years on
6 OP Depot. The study remains ongoing and will
7 remain ongoing for at least another 12 months
8 from this date. At that time, we expect some
9 of the patients to have completed up to five
10 years on OP Depot.

11 This slide is looking at the
12 Kaplan-Meier time to discontinuation for any
13 reason in Study HGKB. And the Kaplan-Meier
14 is used as an estimate because this is an
15 ongoing study. Of course, as Dr. Kane has
16 referred to, the CATIE study used all-cause
17 discontinuation as a useful measure of
18 treatment effectiveness, because it
19 integrates patients' and physicians' overall
20 evaluation of efficacy, safety, and
21 tolerability into a global measure of the
22 balance of the benefits and risks.

1 In the CATIE study, 74 percent of
2 patients had discontinued treatment in the
3 first 18 months. In HGKB, we have much lower
4 rates of discontinuation. At 12 months, only
5 28 percent had discontinued the study, and at
6 18 months, 34 percent of patients had
7 discontinued. These low discontinuation
8 rates were reflected in statistically
9 significant decreases in the PANSS total
10 negative and positive scores.

11 So to summarize the efficacy
12 results for OP Depot, OP Depot has shown
13 efficacy in both acutely ill and stable
14 patients with schizophrenia.

15 There's very robust early and
16 long-term efficacy, similar to the efficacy
17 seen with oral olanzapine. There's no
18 requirement for oral antipsychotic
19 supplementation, and the double-blind
20 clinical studies have not shown a worsening
21 of clinical symptoms if oral supplementation
22 is not used.

1 OP Depot has shown to be effective
2 in treating both positive and negative
3 symptoms of schizophrenia. And there's a
4 flexibility in treatment options, with a
5 variety of effective doses, as well as
6 once-every-two-week and once-every-four-week
7 intervals. Importantly, patients have chosen
8 to stay on olanzapine pamoate depot with low
9 discontinuation rates in all of our clinical
10 studies and encouraging long-term
11 discontinuation rates.

12 That concludes my presentation.
13 Now I'm going to hand it over to Sara Corya,
14 medical director, for a review of the safety
15 of OP Depot.

16 DR. CORYA: Thank you, Dr. McDonnell.
17 Well, as I said before, I'm Sara Corya. I'm a
18 psychiatrist and I treated patients, including
19 those with schizophrenia, for about eight years
20 prior to joining Lilly. I'm currently the
21 global medical director for both Zyprexa and for
22 the OP Depot formulation. In addition to

1 presenting these safety data this morning, I
2 will be moderating for the Lilly group in the
3 question-and-answer session.

4 As Dr. Brophy already mentioned,
5 oral olanzapine has been widely used as a
6 first-line therapy in the treatment of
7 schizophrenia since 1996. And the olanzapine
8 clinical trial safety database includes
9 approximately 12,000 patient exposures. So
10 it was with extensive knowledge of the
11 molecule and in the context of the known
12 safety profile that we examined the safety of
13 OP Depot. Analyses comparing the safety of
14 OP Depot to both placebo and to oral
15 olanzapine were conducted.

16 Safety data were analyzed using
17 three different databases. The
18 placebo-controlled database includes 306
19 patients treated with OP Depot. The
20 olanzapine-controlled database includes 599
21 patients treated with OP Depot. The OP Depot
22 integrated database contains safety data from

1 all 1,915 patients treated with OP Depot from
2 the two blinded studies and six open-label
3 studies. These numbers are slightly
4 different than those presented by the FDA
5 because we have included the data collected
6 over the 120-day period after the original
7 submission.

8 Data for the different OP Depot
9 doses were pooled in all three databases in
10 order to improve statistical power to detect
11 any differences between comparators. The
12 45-milligram dose was not included in the
13 olanzapine-controlled database because it
14 could have led to an underestimate of
15 undesirable effects. It was included in the
16 overall integrated database to present a
17 comprehensive safety profile of all OP
18 Depot-treated patients.

19 By the 120-day post-submission
20 safety update period, 27,210 injections of OP
21 Depot had been given to 1,915 patients, for a
22 total patient years of exposure of over

1 1,400. The longest period of exposure for a
2 single patient at that time was approximately
3 2.6 years, and 241 patients had been
4 receiving OP Depot for approximately one
5 year, including 124 patients receiving
6 two-week injections and 117 patients
7 receiving four-week injections.

8 There are two large ongoing OP
9 Depot clinical trials. And as of
10 September 30, 2007, the total number of
11 injections was 34,825. Reviews of that
12 safety data have shown findings to be very
13 consistent with those in the submission.
14 Some of the safety information I will present
15 regarding the excessive sedation events will
16 be based on exposures through September 30th.

17 I'll begin with serious adverse
18 events, or SAEs. The three databases are
19 listed down the left, and the compared
20 treatment groups across the top. Comparing
21 OP Depot to placebo, the incidence of SAEs
22 observed were quite similar, with 5.1 percent

1 of placebo patients and 4.6 percent of OP
2 Depot patients experiencing an SAE. There
3 was also no statistically significant
4 difference between OP Depot and oral
5 olanzapine in the incidence of SAEs.

6 The incidence in the OP Depot
7 integrated database was higher, as would be
8 expected with the significantly greater total
9 time of exposure.

10 These are the serious adverse
11 events reported in at least five patients in
12 the OP Depot integrated database. Ten
13 percent of the patients had at least one SAE.
14 With the exception of sedation, the most
15 commonly reported SAEs were related to the
16 underlying disease state, such as
17 schizophrenia, psychotic disorder, suicidal
18 ideation, and hallucinations.

19 Moving to treatment-emergent
20 adverse events, here is the comparison
21 between OP Depot and oral olanzapine for
22 events that were reported in at least

1 2 percent of OP Depot patients in the
2 olanzapine-controlled database.
3 Approximately 50 percent of patients in each
4 treatment arm experienced at least one
5 treatment-emergent adverse event. There were
6 no adverse events, with significantly greater
7 incidence in OP Depot than oral
8 olanzapine-treated patients.

9 These are the discontinuations due
10 to adverse events, with the three databases
11 listed down the left and the treatment arms
12 across the top. Discontinuations due to
13 adverse events were low across all databases.
14 No significant differences were observed
15 between OP Depot and placebo, or between OP
16 Depot and oral olanzapine.

17 These are the events that led to
18 study discontinuation in five or more OP
19 Depot-treated patients. Approximately
20 6 percent of patients discontinued from a
21 study due to an adverse event. Less than
22 1 percent of patients discontinued due to any

1 single event. Events that led to
2 discontinuation were consistent with the
3 underlying disease, such as psychotic
4 disorder or schizophrenia, or were consistent
5 with events historically reported in patients
6 treated with oral olanzapine, such as
7 increased weight, somnolence, and diabetes.

8 The primary strategy of our safety
9 evaluation was to compare the safety of OP
10 Depot to that of oral olanzapine. Based on
11 the known profile of oral olanzapine and
12 atypicals in general, several areas of safety
13 were evaluated with special consideration.
14 Overall, the safety profiles were very
15 consistent between the two formulations. No
16 clinically meaningful differences were found
17 with respect to cardiovascular measures or
18 hepatic function.

19 I'll now go into a little more
20 detail on several of the other parameters
21 listed, and then devote the rest of my
22 presentation to injection-related adverse

1 events.

2 Significant within-group mean
3 improvements were seen on each extrapyramidal
4 symptom scale for both treatment groups.
5 These included the Barnes Global Akathisia
6 Scale, the Simpson Angus Scale, and the AIMS,
7 or Acute Involuntary Movement Scale. There
8 were no statistically significant differences
9 between OP Depot and the oral formulation on
10 any of these measures.

11 This figure shows the change in
12 weight over the 24-week period of the
13 olanzapine-controlled trial for both the OP
14 Depot and oral olanzapine treatment groups.
15 The rate as well as the total amount of
16 weight gain over this period was extremely
17 similar between the two groups. In a
18 separate analysis, here, no statistically
19 significant difference was observed between
20 OP Depot and oral olanzapine in the
21 percentage of patients who gained at least
22 7 percent of their baseline weight.

1 Approximately 17 percent of OP Depot and
2 21 percent of oral olanzapine patients gained
3 at least 7 percent of their body weight over
4 the 24-week period.

5 Moving now to fasting glucose, here
6 are the comparisons between OP Depot and oral
7 olanzapine for both mean change in fasting
8 glucose on the left and for the percentage of
9 patients with a treatment-emergent change of
10 at least 10 milligrams per deciliter on the
11 right. No significant differences were
12 observed between OP Depot and oral olanzapine
13 in either of these analyses. There was a
14 numerical difference between OP Depot and
15 oral olanzapine in mean change. However,
16 this did not translate into a difference in
17 the more clinically meaningful
18 treatment-emergent analyses.

19 We'll now look at fasting
20 triglycerides. Here are the comparisons
21 between OP Depot and oral olanzapine for both
22 mean change in fasting triglycerides on the

1 left and the percentage of patients with a
2 treatment-emergent increase of at least 50
3 milligrams per deciliter on the right. No
4 significant difference was observed between
5 treatment groups for either analysis. There
6 was a numerical difference in mean change,
7 although this did not translate into a
8 difference in the more clinically meaningful
9 treatment-emergent analyses.

10 Safety parameters were evaluated in
11 the fixed-dose 24-week study for differences
12 in dose, which were observed for weight,
13 prolactin, and fasting triglycerides. The
14 three different therapeutic doses used in
15 that trial are shown across the top, with the
16 mean changes in weight and prolactin and the
17 treatment-emergent high change in
18 triglycerides shown in each column.

19 Looking first at weight, patients
20 treated with the highest OP Depot dose, which
21 is 300 milligrams every two weeks, had a
22 significantly higher mean increase in weight

1 than those in the 150-milligram group,
2 although not the 405-milligram group. For
3 prolactin and triglycerides, patients treated
4 with the highest OP Depot dose had
5 significantly higher mean changes in
6 prolactin, and a greater incidence of
7 treatment-emergent high fasting triglycerides
8 than patients in the 405-milligram or
9 150-milligram treatment groups.
10 Treatment-emergent high fasting triglycerides
11 was defined as values changing from less than
12 150 milligrams per deciliter at baseline to
13 greater than or equal to 200 milligrams per
14 deciliter at any time.

15 Injection site adverse events were
16 evaluated. Those shown were reported in
17 greater than or equal to 0.5 percent of
18 patients in the integrated database. A total
19 of 8.4 percent of all patients who received
20 OP Depot reported one or more injection
21 site-related adverse events, which is
22 consistent with other IM-administered

1 medications. The most common event was pain,
2 which was generally mild. Overall, there
3 were very few moderate to severe injection
4 site-related adverse events.

5 I'll spend the rest of my
6 presentation sharing information with you
7 about the safety consideration that does not
8 exist with the oral formulation of
9 olanzapine, but that does exist with OP
10 Depot: Events of excessive sedation
11 following injection. As you've heard, the
12 olanzapine pamoate salt is very slowly
13 soluble in muscle tissue, which is what leads
14 to the slow release into the bloodstream
15 after IM injection over the course of two to
16 four weeks.

17 However, it is substantially more
18 rapidly soluble in blood and plasma. So if a
19 portion of the dose comes into contact with
20 blood, olanzapine can go into solution and
21 dissociate from the pamoic acid much more
22 quickly than intended, leading to higher than

1 expected olanzapine concentrations in the
2 bloodstream.

3 We do not believe that all of the
4 excessive sedation events have occurred as a
5 result of direct injection of the OP Depot
6 into a blood vessel by a needle. While this
7 can potentially have occurred in some of the
8 events, it is much more likely that the rapid
9 entrance into the vasculature is a result of
10 vessel injury caused by injection, whereby
11 blood flow pulls pooled OP Depot or pooled OP
12 Depot seeps into the vessel over time.

13 Entrance into the vasculature could
14 also occur more rapidly if an
15 injection-caused vessel injury led to an
16 extravascular bleed around a vessel, but this
17 scenario is much less likely because the
18 volume of blood required to dissolve just
19 20 percent of an OP Depot dose would be quite
20 large, enough to be visible as a hematoma.
21 And we have not had reports of hematomas at
22 the injection site in any of the excessive

1 sedation events.

2 During clinical trials, adverse
3 events were identified in temporal
4 association with OP Depot injection that are
5 consistent with the presence of elevated
6 systemic levels of olanzapine.

7 Symptoms were similar to many of
8 those reported in oral olanzapine overdose,
9 including significant sedation, confusion,
10 and other central nervous system effects. We
11 believe the mechanism for these events
12 involves contact with blood, and we referred
13 to this mechanism in our briefing document as
14 "inadvertent intravascular injection."

15 In their briefing document, the FDA
16 noted a preference for the term "excessive
17 sedation," describing the primary symptom
18 rather than the theoretical mechanism. We
19 understand the rationale for this preference
20 and are open to this, and frankly, other
21 suggestions for terminology. For the purpose
22 of today's discussion, we will be referring

1 to these events as "excessive sedation
2 events." We do think it's important to
3 explain why we believe that contact with
4 blood is the mechanism.

5 First, the clinical presentation of
6 the excessive sedation events has been very
7 consistent with a rapid rise in olanzapine
8 concentration. And the progression of the
9 symptoms over minutes to hours is consistent
10 with the indirect premature entrance of OP
11 Depot into the bloodstream that I just
12 described, as well as the rate of dissolution
13 of OP Depot in blood, which while much faster
14 than in muscle, still requires time.

15 Olanzapine concentrations have been
16 measured in seven of the excessive sedation
17 events, and in each case were elevated. The
18 lack of correlation of those levels with the
19 doses injected suggests that only a portion
20 of the dose is entering the vasculature
21 prematurely. Again, this would be consistent
22 with our belief about vascular injury and

1 seepage into the vessel.

2 In vitro PK and solubility
3 experiments were conducted, showing that OP
4 Depot is indeed much more soluble in blood
5 and plasma than in muscle tissue.

6 Finally, inadvertent intravascular
7 injection is a known risk with IM injections.
8 The IM product that has been most studied in
9 this area is penicillin G procaine, a
10 long-acting formulation of penicillin. And
11 the rate of inadvertent intravascular
12 injection with that product is very
13 consistent with the rate of excessive
14 sedation events that we've seen with OP
15 Depot, suggesting fundamentally similar
16 issues with needles and human anatomy.

17 To be clear, the symptoms a patient
18 will experience after contact with blood has
19 occurred are very dependent on the molecule
20 injected.

21 We considered whether or not
22 reconstitution and administration procedures

1 could be leading to the excessive sedation
2 events. However, based on the training
3 conducted before and again during the trials,
4 and based on the physiochemical properties of
5 the OP Depot suspension itself, there does
6 not appear to be a relationship between this
7 process and the events. Our presentation
8 this morning will include a video
9 demonstration of the reconstitution process
10 where we can discuss this further if needed.

11 We also considered the
12 manufacturing process in our attempts to
13 better understand the mechanism. Used
14 product vials from excessive sedation events
15 were analyzed, and the residual suspension
16 exhibited the expected properties. Also,
17 manufacturing batch records, release data,
18 and stability data were reviewed, and there's
19 been no data to suggest that the
20 manufacturing of OP Depot, either the drug
21 product or the vehicle, may have led to these
22 sedation events.

1 Animal toxicology studies were
2 considered, but were determined to be either
3 infeasible or unlikely to provide additional
4 relevant information.

5 This probably explains why we were
6 unable to find information about animal
7 studies in any of the other IM products which
8 are known to have the risk of inadvertent
9 intravascular injection. While over 15,000
10 IM OP Depot injections were given to animals
11 in our clinical trials, no events of
12 excessive sedation were observed. And an
13 animal study would not further explain how
14 the OP Depot is coming into contact with
15 blood. Injection directly into the
16 vasculature would only confirm what we
17 already know: Olanzapine in the bloodstream
18 causes the symptoms that we've seen in these
19 events.

20 As of September 30, 2007, 2,054
21 patients had received at least one OP Depot
22 injection and 34,825 injections had been

1 administered. Twenty-five excessive sedation
2 events had been reported in 24 patients.
3 Thus, these events had occurred in
4 approximately .07 percent of injections of OP
5 Depot, which translates to about one event
6 for every 1,393 injections, and approximately
7 1.2 percent of patients in the OP Depot
8 trials.

9 The calculated cumulative risk of a
10 patient continuously on OP Depot experiencing
11 at least one excessive sedation event is 0.7
12 to 1.2 percent in the first year of
13 treatment, increasing to 1.6 to 2.3 percent
14 during three continuous years of treatment.
15 These risks are expressed as ranges because
16 the length of the injection intervals varies
17 between two and four weeks.

18 Two additional excessive sedation
19 events have occurred since the September 30th
20 data lock and were shared with the FDA: One
21 in December and one in January. Because they
22 occurred after the development of the

1 briefing document for this meeting, they are
2 not included in the summary statistics.
3 However, we wanted to make you aware of these
4 two events, and to let you know that the
5 clinical presentation of these patients was
6 consistent with what is known about excessive
7 sedation events, that olanzapine
8 concentrations were elevated for each, and
9 that both patients fully recovered.

10 We also want to make you aware of a
11 possible additional event that was reported
12 to our team yesterday afternoon. It has not
13 yet been confirmed, but the description of
14 the symptoms is suggestive of an excessive
15 sedation event. We are evaluating the
16 olanzapine concentration that was collected
17 and investigating conflicting information
18 about the time of onset. As always, we'll
19 share this information with the FDA as it
20 becomes available.

21 Neither the two confirmed events
22 nor this potential event alter the event per

1 injection rate of .07 percent, although the
2 event per patient rate in our clinical trials
3 increased from 1.2 to 1.3 percent, consistent
4 with increasing total time on drug. All 25
5 of these events had an initial onset of
6 symptoms within three hours of injection, and
7 21 of the events had an initial onset of
8 symptoms within one hour of injection.
9 Therefore, of all 34,825 OP Depot injections
10 administered, .01 percent, or about 1 out of
11 every 8,700, have resulted in an excessive
12 sedation event with an onset later than one
13 hour post-injection.

14 Patients who have had these events
15 have experienced symptoms such as sedation,
16 delirium, confusion, ataxia, dysarthria, and
17 fluctuations in consciousness. These
18 symptoms began more mildly and often
19 gradually progressed in severity. Five
20 patients were described as being unconscious
21 or experiencing loss of consciousness. Three
22 of those patients were reported as having

1 been unarousable for a period of time, one of
2 whom was reported to be in a coma, and
3 another of whom exhibited symptoms consistent
4 with coma. As I mentioned previously,
5 olanzapine concentrations were obtained for 7
6 of the 25 events, and in all 7 of those
7 events, the concentrations were elevated to
8 unexpectedly high levels.

9 There did not appear to be a
10 correlation between the dose that had been
11 injected prior to the event and the measured
12 peak concentration, suggesting that only a
13 portion of the injected dose is entering the
14 vasculature prematurely. While one might
15 expect a correlation between injected dose
16 and severity of symptoms, the five cases
17 involving unconsciousness were actually
18 spread across a wide dose range.

19 Twenty patients were hospitalized
20 or visited an emergency room while
21 experiencing an event. Treatment ranged from
22 none in 12 patients to fluids in 5 other

1 patients to additional supportive medical
2 care in the remaining 7, such as
3 benzodiazepines, and 2 cases of urinary
4 catheterization. Two patients were intubated
5 in the course of their care. After IV
6 benzodiazepine administration, neither of
7 these patients experienced respiratory
8 depression. One patient experienced a
9 sustained increase in blood pressure, which
10 responded to antihypertensive treatment.
11 There were no reports of clinically
12 significant decreases in blood pressure or
13 other cardiovascular abnormalities.

14 The time to resolution of symptoms
15 was variable and ranged from 3 to 72 hours.
16 All of the patients experiencing an excessive
17 sedation event did fully recover without
18 permanent sequelae. And 16 of the 24
19 patients elected to continue in the study
20 after experiencing an event. The FDA noted
21 that 17 patients continued after the event,
22 which is correct, but the 17th patient did

1 discontinue prior to receiving further
2 injections.

3 The following is a list of actual
4 terms used by investigators and health care
5 professionals to describe the symptoms of
6 patients experiencing an excessive sedation
7 event. Although this is not a comprehensive
8 list, it does include the most significant
9 terms, and it provides a sense of the
10 clinical presentation of these events. Many
11 of these terms were used for several
12 patients, and the most common presentations
13 involve some degree of sedation and
14 confusion, which we believe is consistent
15 with delirium.

16 I will now describe several of the
17 excessive sedation events in order to paint a
18 more robust picture of the presentation, the
19 treatment, and the outcomes in these
20 patients. All 25 cases were presented in the
21 briefing document.

22 The first patient I'll describe was

1 chosen as an example for two reasons. First,
2 his clinical presentation is very
3 representative of the most common
4 presentation of excessive sedation events.
5 Also, he's the only patient to have
6 experienced an event with two separate
7 injections. He's a 49-year-old male who
8 experienced his first event after receiving
9 his 22nd injection, which was 250 milligrams.
10 He left the site after injection and then
11 returned approximately 60 minutes after
12 injection in a drunken-like state, with an
13 unsteady gait and slurred speech. He was
14 later incontinent of urine. His vital signs
15 were reported to be normal. He was
16 hospitalized for observation, had a normal
17 ECG and CT scan, and recovered after 48
18 hours.

19 He experienced a second event with
20 his 35th injection. Fifteen minutes after
21 that injection, he developed symptoms very
22 similar to those of his first event. He was

1 again hospitalized for observation, was found
2 to have normal vital signs, and recovered
3 without treatment in 72 hours.

4 Olanzapine concentrations from both
5 events were elevated. After the second
6 event, the investigator did elect to
7 discontinue this patient from the study.

8 I had intended to present this case
9 in detail because this patient was reported
10 to have had a seizure and because he was
11 intubated. However, the FDA already shared
12 this case, so I will instead highlight just a
13 couple of important points.

14 Thirty minutes after the injection,
15 this patient became disoriented and agitated
16 and began to experience spasms, also
17 described as involuntary movements, which
18 began in his shoulders and hands and were
19 later termed tonic-clonic convulsions with
20 partial consciousness. He was treated with
21 IV benzodiazepines, Haldol, and promethazine,
22 and was then ventilated as a preventive

1 measure and extubated shortly thereafter.
2 There was no report of respiratory depression
3 at any time, and an EEG was conducted that
4 was normal. It's possible that the
5 involuntary movements were actually
6 manifestations of acute EPS.

7 The FDA also noted another
8 potential seizure in their presentation,
9 although our assessment of that case
10 differed. That patient had what was
11 described as a hyperextension and turning of
12 the arms, which actually persisted into the
13 next day. And we believe this was more
14 consistent with, again, acute EPS than with
15 seizure activity.

16 That said, seizures have occurred
17 in olanzapine overdose at a reported event
18 rate of less than .8 percent. So they are a
19 potential outcome in excessive sedation
20 events.

21 I had also intended to present this
22 case in detail because it involved a patient

1 experiencing a coma. But again, because the
2 FDA did present it, I'll just highlight a few
3 important points. This gentleman left the
4 site 10 minutes after the injection and was
5 found unconscious at a bus stop on a bench
6 approximately 50 minutes after the injection.
7 He later reported that he had been on the bus
8 and hadn't been feeling well, so then he got
9 off the bus and went and sat down on the
10 bench, and that's where he was found. He was
11 in a coma for 12 hours. The treatment he
12 received was IV fluids.

13 Importantly, under the current
14 recommendations for a post-injection
15 observational period, this patient's event
16 would have been identified and addressed at
17 the clinic. Also importantly, the events
18 that I've just highlighted as well as all 25
19 of the events that have occurred were all
20 readily identifiable by abnormalities in
21 mental status, not only by health care
22 professionals, but also by family members,

1 co-workers, the patients themselves, and even
2 the general public. The events are distinct
3 and clearly recognizable as not normal.

4 As I described previously, four
5 events had an onset of symptoms later than
6 one hour after injection. I do want to
7 summarize those briefly here. The first was
8 a 57-year-old male receiving 210 milligrams
9 who experienced sedation at home
10 approximately three hours after the
11 injection. He was weak and sedated and
12 recovered without treatment after about three
13 hours.

14 Second was a 56-year-old female
15 receiving 210 milligrams who left the site 20
16 minutes after injection and was found 75
17 minutes after the injection with malaise.
18 She eventually experienced loss of
19 consciousness and then agitation and was
20 treated with IV benzodiazepines to be
21 intubated in order to perform tests. Those
22 were normal except she did have a urinary

1 tract infection and a positive blood culture.

2 The third patient was a 36-year-old
3 male receiving 405 milligrams who experienced
4 somnolence 90 minutes after injection, which
5 progressed over the course of the next 1-1/2
6 hours to major fatigue, inconsistent speech,
7 and pseudo-delirium. He was hospitalized for
8 observation.

9 The fourth was a 59-year-old female
10 receiving 300 milligrams who experienced
11 somnolence and restlessness 2 hours and 45
12 minutes after the injection. She reportedly
13 remained alert for 3-1/2 more hours, and then
14 experienced profound sedation for 8 hours.
15 She was hospitalized for observation.

16 All four of these patients fully
17 recovered and continued in the study.

18 I won't say much about this slide
19 because, again, it was presented by the FDA.
20 I do just want to point out two things,
21 however. First, you can see that when the
22 concentration is elevated in these events, it

1 tends to come back to normal or to whatever
2 that patient's normal is after about two to
3 three days. And then also, that in this
4 event, in the events we've seen, the
5 olanzapine concentration does not go back to
6 zero. It tends to remain somewhere near the
7 concentration that that patient normally has
8 over the course of the month.

9 As I've described, the symptoms
10 seen in excessive sedation events with OP
11 Depot are generally consistent with those of
12 oral olanzapine overdose. Olanzapine
13 overdose is usually well-tolerated. Typical
14 symptoms are CNS-related, such as sedation,
15 delirium, dysarthria, and ataxia. Less
16 common symptoms include seizures,
17 arrhythmias, cardiac arrest, and respiratory
18 depression. And the reported fatality rate
19 for olanzapine-alone overdose is much less
20 than .01 percent.

21 Three recently published case
22 series of olanzapine overdose of patients who

1 were hospitalized in toxicology units
2 reported commonly observed symptoms similar
3 to those that we've seen with these excessive
4 sedation events, with patients appearing to
5 have fully recovered. Of the 127 cases
6 reported in those case reviews, the only
7 death was attributed to a substantial
8 phenelzine overdose.

9 Because death has been observed
10 with oral olanzapine overdose, it is
11 potentially a risk with the excessive
12 sedation events. However, it should be
13 considered a very exceptional outcome for
14 several reasons.

15 First, as the oral overdose review
16 suggests, a typical course involves full
17 resolution of symptoms. Second, the nature
18 of circumstances surrounding intentional
19 overdoses needs to be considered. These tend
20 to be taken in isolation, at high doses, and
21 with concomitant overdoses of other
22 medications. Conversely, OP Depot will be

1 administered in defined doses, in clinical
2 settings by health care professionals, and
3 patients will be observed on-site for at
4 least one hour for signs and symptoms of
5 overdose, as I'll describe shortly.

6 Analyses were done to determine
7 whether or not certain factors could put a
8 patient at risk for experiencing an excessive
9 sedation event. Three risks factors were
10 identified: Higher dose, lower BMI, and
11 greater age. Keep in mind that higher doses
12 are achieved by the injection of higher
13 volumes, which is likely the connection
14 between dose and risk of an event occurring.

15 It is very important to point out
16 that events have occurred in patients with
17 lower dose, higher BMI, and younger age.
18 It's also important to note that the overall
19 risk is low, even for patients exhibiting all
20 three risk factors. For example, a
21 50-year-old patient with a BMI of 22,
22 receiving a 405-milligram injection, has a

1 .22 percent risk of an excessive sedation
2 event occurring at that injection.

3 All of this information should be
4 interpreted cautiously, as it is based on a
5 relatively small number of events.
6 Importantly, clinicians should follow the
7 precautions and recommendations on the label
8 for all patients receiving OP Depot whether
9 or not they have any of these identified risk
10 factors.

11 The increased risk incurred by a
12 405-milligram injection over a 210-milligram
13 injection is offset by the frequency of
14 injections. For example, the relative risk
15 of a patient receiving 405 milligrams in a
16 single injection compared to a patient
17 receiving 210 milligrams in a single
18 injection is 2.18. However, this changes
19 over the course of treatment if the
20 405-milligram injection is given every four
21 weeks and the 210-milligram injection is
22 given every two weeks, as recommended in our

1 proposed label. Then, the odds ratio
2 decreases to 1.1, indicating that the risk of
3 a patient having an excessive sedation event
4 over time is almost identical for either
5 dose.

6 Additionally, one of our ongoing
7 studies, HGLQ, is a two-year study which
8 allows only four-week injection intervals.
9 Over 2,500 injections have been given to date
10 in that study, and over 2,000 of those were
11 doses of 405 milligrams. There have been no
12 cases of excessive sedation events in that
13 clinical trial.

14 OP Depot has demonstrated a safety
15 profile very similar to that of oral
16 olanzapine, with the important exception of
17 events related to the route of
18 administration. Patients experiencing
19 excessive sedation events with OP Depot
20 presented with signs and symptoms which were
21 consistent with many of those reported with
22 oral olanzapine overdose, and were primarily

1 CNS-related, including significant sedation
2 and delirium. These symptoms were readily
3 identified and observed cases presented with
4 initially milder symptoms, which then
5 progressed in severity over time.

6 Twenty of the 24 patients were
7 hospitalized or visited at an emergency room
8 during the course of their care. Twelve
9 recovered without treatment, five received
10 fluids, and the rest received additional
11 supportive medical care. There were no
12 reported cases of orthostatic hypertension,
13 arrhythmias, or respiratory depression. All
14 patients who experienced an excessive
15 sedation event fully recovered, and the
16 majority elected to remain in the trial and
17 to continue to receive further injections of
18 OP Depot.

19 While we agree with the FDA's
20 characterization of these events as
21 unpredictable in the sense that we cannot
22 reliably predict which patients or which

1 doses will be involved, we do believe that
2 the predictability of onset in temporal
3 association with injection is extremely
4 important, especially with regard to the
5 management of risk. So I'll now describe the
6 risk management plan that we've developed.

7 First, we believe that OP Depot is
8 a critically important medication option for
9 patients with schizophrenia, so we want to
10 find the best way to ensure access to those
11 patients, while addressing the also
12 critically important safety considerations.

13 In other words, we want to find the
14 best way for this medication to be used in
15 clinical practice. It was in that context,
16 and with significant input from practicing
17 psychiatrists, that we developed this risk
18 management plan.

19 The risk management plan has two
20 primary goals: To minimize risk to patients
21 and to optimize favorable outcomes, and also
22 to ensure appropriate identification and

1 reporting of events in clinical practice.
2 There are three main components to the risk
3 minimization piece of our risk management
4 plan: The label, the health care
5 professional educational programs, and the
6 patient/caregiver materials. There are also
7 three main components to the identification
8 and reporting piece of our risk management
9 plan: Tailored pharmacovigilance, the
10 educational programs, and a global
11 observational study.

12 In order to develop an effective
13 risk management plan, it's important to
14 understand who will be receiving the
15 medication, who will be prescribing the
16 medication, who will be administering the
17 medication, and where the medication will be
18 used. Of all of the antipsychotics
19 prescribed, approximately 3 percent are depot
20 formulations. And the primary recorded
21 diagnosis for patients receiving depots are
22 patients with schizophrenia who have a

1 reported history of nonadherence.

2 Approximately 20 percent of
3 psychiatrists prescribe the only approved
4 atypical depot, and the large majority of
5 depots are administered by nurses in
6 hospitals, hospital outpatient centers,
7 community mental health centers, and
8 residential treatment settings.

9 Our risk management plan will
10 include educational efforts directed to all
11 psychiatrists, and enhanced efforts will be
12 directed to the 20 percent of psychiatrists
13 whom we anticipate will prescribe OP Depot
14 and to the treatment settings in which most
15 of this prescribing is done. Depot
16 medications, and especially the atypical
17 depot, are distributed by a limited number of
18 pharmacies which supply them to the treatment
19 centers that I've described.

20 The proposed product label for OP
21 Depot is an integral part of the risk
22 management plan. It includes a bolded

1 warning about the risk of excessive sedation
2 after OP Depot injection. This warning
3 outlines recommendations for a three-hour
4 post-injection precautionary period,
5 including the recommendation that patients be
6 observed by a health care professional for at
7 least one hour after injection, and that they
8 be confirmed to be alert and oriented prior
9 to leaving the clinic. Health care providers
10 should also instruct patients that during the
11 three-hour period after injection, they
12 should be able to obtain assistance if
13 needed, should be vigilant for signs and
14 symptoms of excessive sedation events, and
15 should not drive or operate heavy machinery.
16 This warning provides a description of the
17 signs and symptoms of the events as well as a
18 description of the proposed mechanism.

19 Instructions for the safe use of OP
20 Depot, including a detailed description of
21 proper injection technique, are included, as
22 are recommendations for management if an

1 event occurs.

2 It's important to emphasize the
3 need for individualized patient care during
4 the post-injection period. While it would be
5 very reasonable for clinicians to allow some
6 patients to leave the clinic after one hour
7 of observation because they will be
8 accompanied or will be taking a shuttle back
9 to a group home where they will be in the
10 presence of caregivers, other patients will
11 need to be observed by a health care
12 professional for a full three hours after the
13 injection, such as patients who will be
14 taking a bus home after the injection and
15 will be alone upon arrival.

16 Patients who cannot be relied upon
17 to comply with whatever recommendations the
18 clinician provides with regard to the
19 three-hour period post-injection should not
20 be treated with OP Depot.

21 Our recommendation for clinical
22 management of excessive sedation events is

1 consistent with that of oral olanzapine
2 overdose. There is no known antidote for
3 olanzapine overdose, and the recommended
4 standard of care is to provide treatment of
5 presenting symptoms as medically appropriate.

6 If OP Depot is approved, then after
7 approval, but prior to the time that it is
8 available for clinicians to prescribe, a Dear
9 Health Care Professional letter describing
10 the risk of excessive sedation events will be
11 mailed to all psychiatrists.

12 Invitations will also be sent to
13 all psychiatrists offering regional, local,
14 and single clinic, in-person physician and
15 nurse training programs. The training will
16 include extensive education about the product
17 label, proper reconstitution and
18 administration technique, post-injection
19 observation time, clinical presentation of
20 excessive sedation, management of events, and
21 training of staff. And nurses will practice
22 hands-on reconstitution and administration

1 with a depot nurse trainer. The importance
2 of reporting events will be emphasized, and
3 participation in training will be tracked.

4 Materials, including educational
5 material for the health care professionals as
6 well as materials which they will then use to
7 educate their support staff, patients, and
8 caregivers, will be provided in a variety of
9 media. All promotional programs will include
10 this and other safety information for as many
11 years as promotional programming for OP Depot
12 exists. Additionally, we will enlist the
13 help of professional societies in the
14 education and dissemination of information
15 about OP Depot and the risk of excessive
16 sedation to psychiatrists and psychiatric
17 nurses.

18 The following materials will be
19 provided by health care professionals to
20 patients and their caregivers. A patient
21 package insert, written so that it will be
22 easy to understand, describing pertinent

1 information from the OP Depot product label,
2 will be included in each injection kit. A
3 patient educational brochure, also written so
4 that it will be easy to understand, will
5 describe the excessive sedation risk and
6 possible symptoms, the need for compliance
7 with the post-injection observation period
8 and clinician recommendations, and
9 instructions for what to do should an event
10 occur.

11 External advisors are also helping
12 us develop support tools to be used by
13 patients during the post-injection
14 observation period. These DVDs and print
15 materials will include information about
16 schizophrenia, depot antipsychotics, OP
17 Depot, and recommendations for taking care of
18 general health.

19 Finally, a patient takeaway card
20 will be given to each patient by the health
21 care professional after each injection of OP
22 Depot. This one-page, two-sided information

1 sheet will contain important information such
2 as the phone number for the health care
3 provider and the nearest emergency room, the
4 address of the nearest emergency room,
5 excessive sedation information, and
6 recommendations for what to do should
7 symptoms and an event of excessive sedation
8 occur. This takeaway card will also include
9 patient-specific information, such as
10 concomitant medications and OP Depot doses
11 and dates. And it will be updated by the
12 health care professional with each injection.

13 Finally, the OP Depot web site will
14 provide all pertinent information as well.

15 As I described previously, not all
16 pharmacies distribute depot medications, so
17 our efforts will be directed at those who do.
18 If OP Depot is approved, then after approval,
19 but prior to the time it is available for
20 pharmacists to dispense, a Dear Pharmacist
21 letter, describing the risk of excessive
22 sedation events, will be mailed to all

1 relevant pharmacies and pharmacists. Lilly
2 representatives will visit pharmacies and
3 conduct live educational conversations about
4 OP Depot and the risk of excessive sedation
5 events. And they will provide educational
6 materials containing this information.
7 Visits to pharmacists will occur at least
8 quarterly, and updated information will be
9 provided as available.

10 In addition to pharmacies, poison
11 control centers will be educated about the OP
12 Depot label, the risk of excessive sedation
13 events, and appropriate event management.
14 This will be important, because in addition
15 to medical training, poison control centers
16 are the primary source of information for
17 emergency room personnel in cases of drug
18 overdose.

19 Based on the incidence of excessive
20 sedation events in our clinical trials, 30 to
21 40 events are projected to occur in the U.S.
22 in the first year after FDA approval of OP

1 Depot. It is expected that the close
2 proximity of the events to the injection and
3 the post-injection observational period will
4 facilitate event reporting. The primary goal
5 of the pharmacovigilance plan is to identify
6 the most serious of these events as well as
7 the outcomes that occur. Targeted
8 surveillance terms will be used to guide
9 intensive follow-up of all potential
10 excessive sedation events.

11 The events will be reported and
12 collected through two main channels. The
13 Lilly channel includes field-based personnel,
14 such as sales representatives and medical
15 liaisons, the Lilly call center, and our
16 proposed observational study and all clinical
17 trials. The public channel includes health
18 care professionals, emergency rooms, poison
19 control centers, patients, families, and
20 literature reviews.

21 All identified events will be
22 reported to the FDA. Now, as I said, the

1 primary goal of the pharmacovigilance plan is
2 to identify the most serious of these events
3 and their outcomes. The primary goal of the
4 proposed observational study is to estimate
5 or confirm the incidence rate of excessive
6 sedation events in clinical practice. This
7 study will also further characterize the
8 clinical presentation of these events and
9 possibly identify pertinent risk factors. We
10 will enroll 5,000 patients over two years,
11 and approximately 67 excessive sedation
12 events are predicted to occur.

13 A very important component of our
14 proposed risk management plan is the
15 assessment of its effectiveness in the real
16 world. In other words, how well are we able
17 to identify the events when they occur? And
18 are the outcomes in those events favorable as
19 we anticipate?

20 We will submit quarterly updates to
21 the FDA, summarizing all reports of excessive
22 sedation events. We will evaluate

1 reconstitution and administration error
2 reports quarterly, and modify training if
3 necessary based on those evaluations.
4 Follow-up questionnaires will be sent to
5 prescribers and administrators in a
6 systematized manner to assess recall and
7 understanding of our training and educational
8 efforts. And again, we will modify these
9 programs, if warranted, based on what we
10 learned. Importantly, we will be tracking
11 attendance of health care providers at our
12 training programs, and will direct increased
13 focus to any prescribers or administrators
14 who have not attended but are interested in
15 prescribing OP Depot.

16 Finally, because the observational
17 study will be conducted in the clinical
18 setting by health care professionals who will
19 be educated by the processes I've just
20 described, this study will provide a very
21 systematic forum in which to assess the
22 effectiveness of that educational process

1 through the collection of data.

2 It's our belief that this risk
3 management plan will very effectively provide
4 for the identification and reporting of
5 excessive sedation events, as well as provide
6 for favorable outcomes in patients who
7 experience these events. It's our desire to
8 hear your input and to work with the FDA to
9 determine how this important medication can
10 be appropriately used in clinical practice
11 for patients with schizophrenia who are in
12 need.

13 I would now like to turn the
14 microphone over to Dr. John Lauriello, who
15 will present our conclusions.

16 DR. LAURIELLO: Good morning,
17 everyone. My name's Dr. John Lauriello. And as
18 Dr. Brophy mentioned in the introduction, I've
19 been one of the investigators in the OP Depot
20 studies. I've actually spent my nearly 20-year
21 career doing many studies of new medications,
22 including long-acting agents.

1 But the other major role I have is
2 I'm the executive medical director of the
3 University of New Mexico Psychiatric Center.
4 And that's the largest full-service hospital
5 in the state of New Mexico. And so I want to
6 talk a bit about the medication and then how
7 it would fit in if it was approved in our
8 clinic.

9 Dr. Kane did an excellent job
10 describing the illness. I'll just point out
11 again that this is a very serious illness.
12 And the issue of whether patients take their
13 medications or not, this issue of adherence,
14 has tremendous impact on the patient and
15 often the family and society.

16 Dr. Kane also mentioned the
17 benefits of depot antipsychotics. And having
18 done many trials with depot antipsychotics in
19 my own career, I really do feel strongly that
20 the idea of being able to know exactly
21 whether patients are taking the medications
22 you've prescribed is a very important benefit

1 both to the clinician and to the patient.

2 So I thought I'd start -- we've
3 been hearing some clinical vignettes on the
4 safety side -- I thought I would just
5 describe one of the patients that we had in
6 our clinical trial, HGJZ, that I managed over
7 the span of a couple of years. This is a
8 patient that I had known for many years even
9 prior to starting the study. I knew he and
10 his father through attempting to treat him
11 with other treatments. And frankly, it
12 hadn't gone that well, and the patient ended
13 up in the local jail. And I received a call
14 from the father saying he's going to be
15 released from jail, and I heard about this
16 study and would you be willing to consider
17 him for it. And we did and he met all the
18 inclusion criteria and he was entered.

19 And he did quite well in the study,
20 eventually going into the open-label and
21 being dosed at the 405 every four weeks. And
22 during the 15 months of his open-label time

1 in study, he was able to obtain his GED. He
2 started doing college courses. He was hired
3 for the first time working as an
4 electrician's helper, and he moved out of his
5 dad's home.

6 Just after about 15 months, he came
7 to us in his regular visit and said I'm doing
8 very well, and I would like to be put -- I'd
9 like to convert to the oral antipsychotics.
10 And it seemed like a reasonable option. This
11 happens all the time, patients move back and
12 forth from these types of treatments. And so
13 he was put on an oral antipsychotic.

14 And I received a call a couple of
15 months later from the electrician he was
16 working for and said I can't have him work
17 for us anymore. He's just not attending to
18 the things that he needs to do, and it's,
19 frankly, dangerous. And since then, he's
20 really had a full relapse, and we've had a
21 lot of difficulty getting him back to the
22 baseline we had while he was in the study.

1 The father called me and asked me
2 would there be a chance that he could go back
3 on the OP Depot. And I said because it's a
4 study, at this point, he couldn't. But I
5 think he's a very typical kind of patient
6 that we would think of when we think of
7 managing patients with OP Depot.

8 So I mentioned we have this very
9 large psychiatric center. And in this
10 psychiatric center, we have a depot or
11 injection clinic. There's a medical director
12 and several nurses that work in this clinic.
13 And I think that's very typical for large,
14 public sector hospitals like ours. We're
15 both the county and the university hospital
16 at the same time.

17 And you see here that at this
18 point, this is a snapshot at the end of 2007,
19 that roughly a third of the patients are on
20 each of the available long-acting agents:
21 Fluphenazine, haloperidol, and risperidone.
22 We see, though, that there's a limitation to

1 how far we can use the current available
2 options. For the typical antipsychotics and
3 in contrast to the oral world where very few
4 antipsychotics are used, long-acting agents
5 still use a lot of typical. You see
6 two-thirds of the patients are taking
7 typicals. What we see is that we have to
8 struggle with an increased rate of
9 extrapyramidal symptoms. And as Dr. Kane
10 mentioned, we are very concerned about the
11 potentially higher risk of tardive
12 dyskinesia.

13 Risperdal long-acting injection,
14 also called Risperdal Consta, has been a real
15 welcome addition to our clinic. I think this
16 has invigorated the clinic to some extent in
17 terms of having an atypical agent to
18 complement the older typicals. But there are
19 limitations to how well we've been able to
20 use this medication as well.

21 As Dr. McDonnell mentioned, it has
22 this unusual way of needing to have a long

1 supplementation period because the drug
2 really doesn't kick in because the
3 microspheres do not give out drug until about
4 three to four weeks. And so you have to
5 figure out, and we've learned to do this in
6 different ways, how to deal with this lead-in
7 period of time when the injection has not yet
8 kicked in.

9 On the inpatient wards, there's
10 been a fair amount of resistance. We run
11 three big inpatient wards, and there's been
12 some resistance to the use of risperidone
13 long-acting because ultimately the doctors
14 tend to think in the time frame that they
15 manage the patient, which is usually the
16 average length of stay for a patient. With
17 schizophrenia in our institution it's
18 about -- between maybe 6 to 10 days. And if
19 you gave an injection, that injection would
20 not kick in until about 21 days. So we would
21 like to see more patients get started in the
22 hospital, but that doesn't seem to happen as

1 much.

2 The other thing that we need to
3 always remember is that while studies have
4 shown that all these medications tend to do
5 about the same in trials, individually,
6 patients are very particular in which
7 antipsychotics they respond to. And so we
8 see that in the oral world, we have six
9 atypical antipsychotics, and we use all six
10 of the available ones now to tailor
11 medication efficacy to any particular
12 patient. And we only currently have three in
13 the depot world.

14 So how would we put OP Depot into
15 our clinic? Well, I mean, I think we would
16 first factor in that we know that olanzapine
17 has been a proven antipsychotic that we've
18 used for many years. I think the idea of
19 another atypical would be extremely important
20 to us. I think there's a large group of
21 patients that we would like to give an
22 atypical long-acting who probably would not

1 necessarily respond to risperidone that could
2 respond to olanzapine.

3 We are very much interested in the
4 fact, and we've seen it in our own practice
5 as researchers, that this drug has early
6 effects. So I think this would be an
7 extremely appropriate drug to use on the
8 inpatient service, because within three days,
9 you're going to start to see effect. And I
10 think it's much easier for inpatient
11 physicians to think about this drug in terms
12 of how it would be started in hospital.

13 Everybody has mentioned the ability
14 to use it from two to four weeks. I think
15 this is critically important. Our goal, my
16 goal, when I manage patients in these clinics
17 is to try to get the patient to the longest
18 possible interval that works for them. So
19 for some cases, it has to be every two weeks,
20 but in many cases it could be every three or
21 four weeks. And this is a real advantage in
22 terms of managing patients.

1 Dr. McDonnell mentioned the
2 flexible dosing. And what he meant is that
3 not just interval, but that the dose can be
4 graded in a way that we're used to doing with
5 haloperidol and fluphenazine, which you're
6 not really able to do with risperidone
7 because that's a unit dosing. And in our
8 practice using this drug in the open-label,
9 we've really used this idea of being able to
10 take increments of 15 milligrams, that's .1
11 CCs equals about 15 milligrams. And so for
12 some patients, we've slowly increased the
13 dose using this method, and other times we've
14 slowly decreased the dose. You'd be
15 surprised how many patients would be willing
16 to accept 285 every two weeks versus 300
17 every two weeks, even though maybe that's not
18 exactly a big difference, but for the patient
19 to have some control, again, over the dosing.

20 The risk of the olanzapine
21 treatment, we've talked a lot about that in
22 the previous talk, but we really take

1 seriously that there is some -- there is risk
2 of olanzapine, whether you give it in
3 injection or whether you take it orally. We
4 know that it has a propensity for weight
5 gain. We know that we'll have to do
6 monitoring of glucose and triglycerides and
7 manage people. And so the psychiatrists and
8 the team that works in the depot clinic is
9 really going to have to be aware and be
10 active in monitoring all those side effects
11 and make intervention as necessary, including
12 taking patients off if it's not acceptable.

13 The excessive sedation events: we
14 currently have about 225 patients in the
15 clinic, so we will probably have about, in a
16 year or so, we could easily have 82 patients,
17 so we'd expect one case in that group of this
18 excessive sedation. So we're expecting that
19 we will need to be prepared to deal with
20 this.

21 I think Lilly has done a very good
22 job of thinking about this plan for how to

1 educate. I would expect that everybody in
2 our clinic would be well-trained. I think we
3 will have to change the way we do our clinic
4 for patients who are taking this medication.
5 Right now, if a patient shows up and needs a
6 shot, we will often just give them the shot
7 because we want to be able to take the
8 opportunity to give them the treatment. But
9 we wouldn't do that in this case.

10 If a patient -- we would expect
11 patients to come earlier in the morning, so
12 we'd have both the possibilities of the
13 three-hour time frame, but also if something
14 happened, time in the day to deal with it.
15 We'd also expect that if a patient comes to
16 us and says -- you know, we ask them are you
17 able to stay for as long as three hours, and
18 they say, well, in 20 minutes I have to go
19 register for classes, I mean, our reaction
20 would be, hooray, you're registering for
21 classes, but you can't get the shot today.

22 And so I think we would do

1 something a bit differently than we do
2 currently with the other ones.

3 This idea of potentially giving the
4 flexibility for an hour stay or a three-hour
5 stay is very attractive to our clinic. I
6 think we would initiate some sort of checkout
7 in which our expectation is that patients
8 after an hour, if nothing had happened, we
9 would expect that they'd have to be
10 accompanied by someone, and there'd have to
11 be a guarantee that that person would stay
12 with the patient. That could be the case
13 manager, that could be the family. We would
14 not be comfortable releasing people just to
15 go on their own after one hour. We would ask
16 them to stay for the whole three hours.

17 So overall, I just wanted to kind
18 of bring the context of the clinic to our
19 discussion. The word "catastrophic" is not
20 an underestimation of what happens when
21 patients are not treated for this illness.
22 We have seen devastating effects to the

1 person, to their family, to people they don't
2 even know when patients are unmedicated. You
3 know, for us who are in the field, I mean,
4 the idea of the risk-versus-benefit ratio is
5 really skewed towards we really need to get
6 the patients treated, and we think we have
7 ways to manage the risks. We don't really
8 have great ways to manage people unmedicated
9 out there doing poorly. That doesn't work so
10 well for us.

11 I think OP Depot is an important
12 addition. I think it will help for patients
13 who cannot respond to the available
14 long-acting agents. I think we'll be taking
15 very seriously the side effect profile that
16 we've just heard about. We expect the
17 company to be aggressive in terms of training
18 and teaching, and our obligation is to take
19 that training and learn it very well.

20 So with that, I'll stop.

21 Thank you.

22 DR. CORYA: The FDA asked us to

1 develop a short video to show to all of you
2 today to address a couple of the questions that
3 they had. One is around the reconstitution
4 process and what that looks like, and again,
5 concerns about whether or not that could be
6 involved with the mechanism for the excessive
7 sedation events. And then also, whether or not
8 if blood is aspirated into the syringe, because
9 it's a fairly opaque material, would that be
10 visible? Would nurses know as they're drawing
11 back for the aspiration that blood -- that they
12 actually had entered a vessel?

13 So we have a short presentation to
14 show you and here it is.

15 (Video is shown)

16 DR. CORYA: That does conclude Lilly's
17 presentation.

18 DR. RUDORFER: Thank you. The
19 presentations and video were very helpful and
20 informative. And we're now open to clarifying
21 questions from the Committee.

22 Dr. Geller?

1 DR. GELLER: A few questions. First,
2 I want to thank Dr. Kane and the others for just
3 a very excellent description of the clinical
4 problem that we all face. One of the things in
5 the material, if I read it correctly, is that
6 after a few weeks, the dose lowers. And perhaps
7 you can tell us if I'm reading the material
8 correctly. And if that's the case, how would
9 clinicians be educated to do that?

10 And then two parts of data that I
11 didn't see in the briefing materials that I
12 think it's important for us to examine. The
13 QTC interval; it was said there were eight
14 cases of concern. Perhaps we can see the
15 mean and standard deviations on the QTC, and
16 more details about the eight cases of
17 concern. And similarly, if we could see mean
18 and standard deviations pre and post on
19 triglycerides and prolactin.

20 DR. CORYA: Okay. First, I want to
21 make sure that I fully understand your very
22 first question. You were saying that there's

1 something that has led you to believe that
2 the --

3 DR. GELLER: Is the dose the same
4 throughout? When somebody is given an initial
5 dose, is that the dose they're receive ongoing?

6 DR. CORYA: Not necessarily.

7 DR. GELLER: Can you give us a little
8 more detail about that?

9 DR. CORYA: So you mean the actual
10 prescribed dose that's being given, not the
11 concentration that's in the patient over time?

12 DR. GELLER: Right.

13 DR. CORYA: Well, just as with the
14 oral formulation, that's very much a clinical
15 decision. So the dose can be raised or lowered,
16 much as you would with an oral formulation,
17 depending on the symptomatology of the patient.
18 So a patient could -- and we have seen in the
19 clinical trials, the KB study, the long-term
20 ongoing study, where patients were dosed, they
21 got one dose at one visit and if they weren't
22 doing well enough, then clinician thought they

1 needed a higher dose the next time.

2 Okay, then I think your next
3 question was around QTC. I believe we have a
4 slide that looks at mean change. Okay. We
5 have several slides, so I'll have to see if
6 we can find the one that fully answers your
7 question. But this is looking at the
8 corrected QT interval, corrected
9 appropriately for the slight increase in
10 heart rate that you see with olanzapine.

11 Looking at the OP Depot integrated
12 database, this contains all the OP Depot
13 data, with the N of a little over 1,900 as
14 you see there, looking at different time
15 periods and looking at the mean changes at
16 different time periods. So you can see a
17 slight decrease in the QT interval at both 24
18 and 48 weeks. At 72 weeks, that is the
19 longest mean change that we see, and then a
20 smaller change at the longer term, at 96
21 weeks. Now, there are fewer patients at the
22 96 weeks as well.

1 We can also look at
2 treatment-emergent adverse events that were
3 cardiovascular-related. And what you're
4 looking at here are the adverse events in the
5 olanzapine-controlled database so that we can
6 compare what we know about OP Depot to oral
7 olanzapine, because of course, we know a lot
8 about oral olanzapine use over time with
9 regard to QTC and cardiovascular events.

10 So you've got the depot here on the
11 left and the oral on the right. And you can
12 see down the left the various reported
13 adverse events in patients over the course of
14 the clinical trial. Basically, we saw that
15 the adverse events were very similar to what
16 we've seen with oral olanzapine since 1996.
17 There were no surprises there.

18 DR. GELLER: Could you show us the
19 mean and standard deviations of the actual
20 values of the QTC before and after treatment?

21 DR. CORYA: I think so. So QTC
22 without looking at the long-term data. Just

1 mean QTC? We may have to get that after the
2 break. I apologize.

3 DR. GELLER: And the same for the
4 triglycerides.

5 DR. CORYA: Yes, we do have that. Why
6 don't we first look at the core slide for
7 triglycerides? Again, this is comparing -- this
8 is looking at potentially clinically significant
9 treatment-emergent changes in fasting
10 triglycerides, looking at the mean change in the
11 24-week study. So the mean change, I think
12 unusually here, for triglycerides, there on the
13 left for the OP Depot went down. That's not
14 really what we would expect. Normally we would
15 see an increase in triglycerides on mean change,
16 as we saw there with the oral formulation. And
17 then when you look at the treatment-emergent
18 changes, which is where you've got a change of
19 50 milligrams per deciliter, any patients who
20 had that change over the course of the 24 weeks
21 are there on the right.

22 And you can see that it was very

1 consistent between the two formulations, and
2 actually very consistent with what we have
3 seen historically with oral olanzapine and
4 with the information that is currently
5 contained in the Zyprexa product label.

6 DR. GELLER: I'm sorry, I'm not being
7 clear. I think we'd like to see the actual
8 values with their standard deviations at
9 baseline and then post-treatment.

10 DR. CORYA: So here, we're looking at
11 the ECGs, mean change from baseline to endpoint,
12 again in the olanzapine-controlled database. So
13 we've got all the different intervals, including
14 the QT. I would call your attention again to
15 the QTC corrected -- Fridericia correction
16 factor, because that's appropriate for
17 olanzapine. And you can see the baseline values
18 for both depot and oral here, and then what the
19 mean change was for -- it actually went down, I
20 guess, a little bit for the OP Depot-treated
21 patients and then slightly up for the oral
22 olanzapine-treated patients.

1 DR. GELLER: Where are the eight cases
2 of concern --

3 DR. CORYA: Yes, I'm not -- which
4 material did you see eight cases of concern?

5 DR. GELLER: On page 38 of the FDA
6 briefing materials, it mentions -- there's a
7 paragraph which says there were eight patients
8 with potentially clinically significant QTC
9 observations.

10 One patient randomized to OP Depot
11 300 milligrams -- Q 2 weeks had a QTC
12 interval over 500 milliseconds. Six patients
13 had an increase over 60.

14 But without seeing what the actual
15 value is, it's hard to be fully informed.

16 DR. CORYA: Okay, thanks for that
17 clarification. Yes, there are different ways
18 you can measure whether or not QTC with -- going
19 in a certain patient, if it's over a certain
20 threshold, that might be I guess of concern.
21 And those values are a little bit different for
22 males and females, but there's sort of a

1 standard threshold whereby above 500, that that
2 is considered potentially clinically
3 significant. We did have a case of that. That
4 patient did not have any adverse events
5 associated with that. It appeared to be a
6 nonsymptomatic increase in QTC.

7 Again, that is not unusual for
8 treatment with olanzapine. In this large of
9 a patient base, we did not see any more
10 increases in QTC or any more cases of concern
11 or cases going above 450 or 470, again
12 depending on if it was males or females, in
13 these clinical trials, and we have seen
14 historically with olanzapine. There is
15 sometimes a small increase in QTC, but very
16 uncommon for the events to go above those
17 potentially clinically significant amounts.
18 I can get you the exact numbers in the
19 clinical trials for how many patients did,
20 perhaps after the break.

21 DR. GELLER: Right. The concern -- I
22 don't want to belabor this too much. On the

1 other hand, the concern with haloperidol and
2 thioridazine is that there may be a significant
3 cardiovascular risk. And here, it differs from
4 oral, because you're putting in a medication
5 that's then going to be there for several weeks.
6 So if there were any QTC concern, it would be
7 greater with the IM than it would be with the
8 oral.

9 DR. CORYA: I think that that's
10 absolutely a very legitimate concern. Again, we
11 do have a lot of experience with olanzapine over
12 the past 11 years, and we know that potentially
13 clinically significant events above the 500 that
14 you mentioned are very uncommon, about .1 to
15 1 percent of the patients. And we also know
16 from our clinical trials comparing the oral
17 formulation to the depot formulation that we
18 have not seen, at least in our clinical trials,
19 any difference between the two formulations with
20 regard to QTC parameters.

21 DR. RUDORFER: Dr. Shaffer had a
22 question.

1 DR. SHAFFER: I guess there are four
2 potential challenges to the idea that this may
3 be an accidental intravascular injection effect.
4 One is the case of the delayed onset. The
5 second is the absence of a training effect. The
6 third is the individual who had repeated
7 occurrence.

8 And then I don't know if this means
9 anything, but in the one demonstration of the
10 concentrations that you gave, there seem to
11 be no lower pre-repeat injection
12 concentration for the individual who may have
13 lost a substantial volume of substance at the
14 time of the initial injection. And I just
15 wondered what is made of these challenges
16 if -- or if they are challenges -- and what
17 are alternative explanations?

18 DR. CORYA: So is that a question
19 directed to me or --

20 DR. SHAFFER: It seems to me that the
21 mechanism is being proposed by the company
22 rather than by the FDA.

1 DR. CORYA: So I'm not sure if I'm
2 understanding the question.

3 DR. SHAFFER: The question is, you
4 proposed a pathology, but not all of the facts
5 fit the pathology. And I just wondered if there
6 are alternative explanations for why this might
7 occur.

8 DR. CORYA: We've certainly tried to
9 think of them. And as I mentioned in my
10 presentation, I pretty much mentioned in my
11 presentation every idea and theory that we've
12 had and every investigation into other
13 mechanisms that we've been able to come up with.
14 You know, we're certainly open to other ideas
15 and other things that we might do, but we have
16 not -- despite extensive research into it, been
17 able to come up with any better explanation.
18 And while I think that there are some pieces of
19 information that don't necessarily fit, I don't
20 know that that there are any pieces that really
21 would refute what it is that we're saying is our
22 mechanism.

1 For instance, one that starts
2 later. You know, you're absolutely right,
3 that's concerning the one that started at
4 2 hours and 45 minutes. But again, I
5 actually think that's consistent potentially
6 with a vessel injury, where you've got a
7 little bit of an injury there, but it's going
8 to take a while for that -- the pool -- the
9 olanzapine depot to actually get into the
10 bloodstream and then dissociate from the
11 pamoic acid and then become available across
12 the blood-brain barrier, et cetera. So if it
13 is a slow leak from a small injury to a
14 vessel, one could envision how that could
15 occur.

16 DR. RUDORFER: Dr. Winokur and then
17 Dr. Mann.

18 DR. WINOKUR: I have a couple of
19 questions related to concomitant medications, so
20 I'll start with the first, then maybe a
21 follow-up or two.

22 In the identified 24 patients who

1 had the extreme sedation incidents, what
2 information is there about concomitant,
3 especially seen as active medications in
4 those cases? I gather some were from the
5 open-label extension where concomitant
6 medications could have been part of the
7 regimen.

8 DR. CORYA: Yes. Let me show you
9 exactly what the patients were taking. So here,
10 we've got all of the 25 events, and their
11 concomitant medications are listed. I might
12 call your attention to a couple of those.

13 Patient No. 5 is the same gentleman
14 as Patient No. 8, who had the two events.
15 And he was taking aspirin at the time of both
16 of those events, so potentially that could
17 impact bleeding at the injection.

18 Other than that, we didn't see a
19 whole lot with regard to the mechanism. We
20 did -- you know, several of the patients were
21 on benzodiazepines. And so what we did was
22 we did an analysis to see was there any risk

1 involved with being on benzodiazepines and
2 getting an event. And we actually found that
3 there was not. There's no more likelihood of
4 a patient getting one of these events or
5 having an event if they're on a
6 benzodiazepine than if they're not.

7 Also, if they are on a
8 benzodiazepine at the time of the event,
9 there's no correlation between the ultimate
10 severity of the event and the dose that they
11 were taking. There might be one exception to
12 that. This patient here had actually taken
13 4 milligrams of unprescribed clonazepam about
14 eight hours prior to the injection. Now, she
15 was not reported to be tired at the time of
16 the injection before she got it, but she
17 ended up becoming quite sedated with her
18 excessive sedation event.

19 There was a little question at that
20 site as to whether or not she might have
21 actually ingested other Klonopin at the time;
22 they were never sure. So conservatively, we

1 determined that probably she had not, but
2 that was a possibility.

3 But in general, even if they have
4 other psychiatric medications on board that
5 are potentially sedating, the overdose, if
6 you will, of the olanzapine sort of trumps
7 the side effects that you would have from
8 anything else. That really tends to
9 overwhelm what else that they would be
10 taking.

11 You know, that said, obviously
12 concomitant medications, especially those
13 with CNS effects, should be considered.

14 DR. WINOKUR: And then a related
15 question. I know this wasn't part of the study,
16 but at least to hear you and your colleagues'
17 thoughts, what about concomitant use of
18 essentially metabolic inhibitors? So drugs that
19 people might be on that would inhibit 1A2 or
20 2D6, and then have this pronounced episode with
21 a marked increase. Has there been any thought
22 to how that might impact on the potential impact

1 of the whole situation?

2 DR. CORYA: There are two medications
3 that seem to be impacted from what you're
4 describing. Fluvoxamine is one of those and
5 Tegretol, or carbamazepine, is the other one.
6 So those would be the two medications. I can
7 never remember which one's lowering or raising
8 olanzapine or it's lowering or raising them.
9 But those are the only two drugs that have been
10 studied in conjunction with olanzapine where
11 there's been an impact on the actual
12 concentration of one or the other.

13 DR. WINOKUR: And my final question
14 I'll ask for now, going from the clinical trial
15 world to the real world, where we know that
16 polypharmacy is very common, certainly in my
17 part of the real clinical world, do you have any
18 thoughts about how we -- certainly in talking
19 with the FDA about the potential impact of these
20 kinds of episodes, might play out in a much more
21 complicated, with much more CNS concomitant
22 medication-type circumstance?

1 DR. CORYA: Yep, that's a very good
2 question, and we've thought a lot about that.
3 First of all, I think one of the -- we're
4 worried about that, too, and so one of the
5 things that we're doing is not only the
6 pharmacovigilance, but the observational study
7 that I described where we're going to be able to
8 collect exactly that information and better
9 understand is there something else that we need
10 to be worried about with regard to that.

11 In the KB study, the long-term
12 ongoing study right now, we are actually
13 allowing the use of other CNS medications,
14 not antipsychotics, but mood stabilizers and
15 antidepressants. And we've always allowed
16 benzodiazepines in our clinical trials. So
17 we do have a fair amount of information
18 already collected on concomitant medication
19 use. Yes, it might be higher outside the
20 clinical trial setting, and we fully intend
21 to be watching that very closely to determine
22 whether or not something needs to be done

1 differently from a management standpoint with
2 regard to that.

3 DR. WINOKUR: If I can just ask one
4 final -- can I just ask, maybe after
5 consultation with your colleagues, have a little
6 more discussion about the metabolic inhibitors
7 and potential drug interaction issues?

8 DR. CORYA: Yes, I can have
9 Dr. Berkstrom join me right now.

10 DR. BERKSTROM: I'm Rich Berkstrom at
11 Eli Lilly and Company, a pharmacokineticist.
12 It's certainly true that olanzapine is
13 metabolized by cytochrome P450 1A2, and
14 inhibitors of this enzyme do increase the
15 concentrations of olanzapine. If an individual
16 were taking an inhibitor like fluvoxamine, which
17 is an inhibitor of 1A2, they would likely have
18 already high concentrations of this drug. And
19 hopefully, their dose would have been adjusted
20 during the routine clinical trial -- or routine
21 clinical management of their disease so that
22 they would not -- would be tolerating the

1 appropriate dose.

2 But if the event occurred, I'm not
3 sure that it would really affect the onset of
4 the event so much, because obviously, this is
5 a rapid entry into the bloodstream, high
6 concentrations. It may impact the duration
7 upon which the event resolves. However, we
8 see that these events resolve fairly quickly
9 over time; in other words, in several days,
10 probably because of rapid redistribution of
11 the drug rather than its metabolic clearance.

12 DR. RUDORFER: Thank you.

13 Dr. Mann?

14 DR. MANN: A couple of -- I have a
15 comment which relates back to the original
16 question about the frequency of the excessive
17 sedation events per injection. And I'm not sure
18 if I understand Lilly's approach to this
19 problem, but I do understand that we don't have
20 very much in the way of data, and maybe that's
21 important.

22 But if you hypothesize that there

1 are certain fixed risk factors, like you're
2 using an 18-gauge needle which may be a bit
3 bigger than other formulations, or the volume
4 plays a role, and assume that's relatively
5 constant over time, then you would expect a
6 constant risk factor -- a constant risk
7 manifesting itself over time.

8 And while I'm not sure that I
9 understood all of the details of the time
10 course of appearance of this event, it does
11 say that the first -- that the mean time to
12 the first event, which is usually the only
13 event in most of your patients, is about
14 eight months, and 18-plus injections. So I
15 think it's crucial to understand whether the
16 risk is appearing accumulatively over this
17 period and half -- you know, a lot of the
18 risk is distributed on either side of this
19 time point of eight months and 18 injections
20 or not.

21 Because if it isn't constant, but
22 there is an increase in the rate over time,

1 then that indicates that there's some change
2 in the risk factors that are operating. And
3 that change, one could speculate, could
4 either be a change in the administration,
5 maybe staff is changing, maybe training is
6 declining -- it looks pretty finicky from
7 that video getting that solution dissolved
8 just right -- or there could be a host
9 change. Maybe there's an alteration after
10 all those injections in the vasculature
11 around the injection site, and maybe you have
12 biopsy data that could comment on that, or
13 maybe we should be getting biopsy data to see
14 if that's true.

15 So hopefully after lunch, we'll see
16 whatever you can generate in terms of the
17 risk rates, which I think are the only thing
18 that are informative compared to just giving
19 absolute numbers.

20 The second comment I have is
21 related -- is a question really from
22 Dr. McDonnell, and I wonder if he could

1 relate this to this whole issue of the
2 formulation and why this formulation carries
3 this risk and other formulations for other
4 drugs don't have the same risk -- for
5 example, decanoate or et cetera. And that is
6 that you pointed out that the peak level for
7 OP is somewhere in the first week, and that
8 matched up with fluphenazine or haloperidol
9 also around the first week, but there is a
10 difference.

11 One is that the peak level for OP
12 seems to be around Day 2 after an injection.
13 But the peak level after those other drugs
14 seems to be around Day 7. Now that may be
15 advantageous, as you also point out, because
16 you're getting some indication of separation
17 from placebo very early on. But I wonder
18 whether the actual formulation itself being
19 so rapidly available, in addition to the
20 acceleration when it comes into contact with
21 blood, may explain part of the risk pattern
22 that you're seeing in terms of the excessive

1 sedation.

2 DR. CORYA: Let me take these one at a
3 time, and I will ask for some help from the
4 group.

5 First of all, with regard to the
6 other products that have not had these
7 events, that is correct. And we believe that
8 there are two major reasons for that. First,
9 because of what you've sort of already
10 described, it's a different formulation.
11 There are oil-based products and there are
12 microspheres and then there is this salt.
13 And certainly the rate of dissolution is very
14 affected by that.

15 So even if another drug were to be
16 injected into the vasculature or around the
17 vasculature like we've described, they would
18 not necessarily have the rapid increase of
19 the free drug in the bloodstream to cause
20 these symptoms. Even if they did, they
21 wouldn't necessarily have the same symptom
22 profile.

1 I mean, olanzapine is known for
2 being a very, very sedating medication. And
3 so again, they wouldn't necessarily have the
4 strong marker that we have seen with this
5 medication to show that that's occurring. So
6 we don't really know whether or not they're
7 occurring with those other medications, but
8 certainly if they are, they're not causing as
9 much of a problem for the patients as we've
10 seen with our product.

11 With regard to -- I'll let
12 Dr. McDonnell in a moment talk about the two
13 days and the other products that you were
14 mentioning, if need be. Just a couple of
15 things about the risks. We could wait until
16 after lunch, as you suggested, or we could go
17 ahead and try to provide more information for
18 you about the cumulative risk over time.

19 You're right, the risk does go up
20 over time. But that appears to be a factor
21 of with each injection, you're going to have
22 a risk. I'm going to ask our statistician to

1 come up and explain the statistical model
2 that was used to calculate that risk.

3 DR. ANDERSON: My name is Scott
4 Anderson. I'm a senior research scientist in
5 statistics at Eli Lilly. The risk factor
6 analysis we did actually included variables that
7 change at the time of the injection. So the
8 study dose was something that is flexible. Most
9 of the events occurred in KB, so the dose was
10 not fixed for a given patient. BMI was also a
11 risk factor that was moving as the injections
12 went on.

13 In terms of whether or not the more
14 injections you get, was that a risk factor,
15 we did have one patient who did get the event
16 after their first injection. We had another
17 patient get the event after their second
18 injection. When we did some exploratory
19 looks at the number of injections as a
20 potential risk factor, we could not find
21 anything significant there.

22 DR. RUDORFER: Dr. Follmann was next,

1 and then Dr. Potter.

2 DR. FOLLMANN: Thanks. I had a couple
3 questions I wanted to bring up. First of all,
4 related to the risk factors for the sedation
5 events, I was wondering if you considered
6 clustering by technician. So you mentioned you
7 had one patient who got two sedation events. It
8 could be that that patient was given a shot by
9 the same technician. And so in some of the
10 other analyses you talk about is clustering
11 events by patient. Maybe it's really more by
12 technician. That would I think fit more with
13 the hypothesis that it's related to
14 administration. So I was wondering if you'd
15 looked at that.

16 DR. CORYA: The closest that we did
17 come to that was looking at clustering by site,
18 the investigative site. And we found that there
19 were three different sites over the course of
20 the clinical trials who each had two different
21 excessive sedation events. The one was in the
22 U.S., and that was the gentleman who had two

1 events. And probably that had as much to do
2 with a risk factor within that given patient
3 that we don't fully understand as it did the
4 person giving -- administering the product. We
5 do not know necessarily whether it was the exact
6 same person who gave the injection at those
7 other two sites where they had the events.

8 DR. FOLLMANN: If you had the
9 technician-level information, you could do some
10 probability calculations to determine how likely
11 or unlikely it was, so maybe that's something to
12 do in future.

13 The other thing that has to do with
14 risk, and also actually clustering, relates
15 to your slide 57, and also your slide 77.
16 But I think slide 57 might be the simplest
17 point at which to describe the issue. In
18 that slide, you report risk of experiencing
19 sedation events per patient over different
20 periods of time.

21 That's not the slide I was -- oh,
22 yeah, it is. It's on the bottom there. So

1 at the very bottom, you have risk of event
2 over one, two, or three years. And my
3 understanding of this is this is based on a
4 particular statistical model. And if you do
5 a different model, you might get a different
6 answer, actually. And I think this model is
7 based on the idea that sedation events
8 cluster within individuals, and so it's not
9 like everyone is flipping a coin with chance
10 1-over-1,000 at every injection of getting an
11 event. It's more like you have winners and
12 losers. Some patients are very likely to
13 have this event and others are very unlikely.

14 My question has to do with what is
15 the evidence for doing this model that
16 assumes there are sort of winners and losers
17 in terms of the patients in terms of the risk
18 of an event per injection?

19 DR. CORYA: Okay. Scott?

20 DR. ANDERSON: Just as you said, the
21 strongest evidence is the fact of the one
22 patient having two events. We know that patient

1 was not administered the drug by the same person
2 during those two events, so we ruled the
3 technician part of it out for that. And then
4 also the risk factor analysis, the fact that
5 certain patients have higher risks seemed to
6 indicate to us then that a beta-binomial was an
7 appropriate model.

8 DR. FOLLMANN: I would just -- you
9 know, I thought about this a little, and so I
10 noticed your calculation about how unlikely it
11 was that one patient would have two sedation
12 events, and I think that's true. But the issue
13 is if you have 1,000 patients, having a cluster
14 is not that unlikely. And so I think it's still
15 an open question as to whether this clustering
16 effect is going on or it's really more like you
17 just flip a coin, with 1-over-1,000 chance at
18 every injection. I think it's not clear.

19 But if you consider that other
20 model, the coin-flipping model basically, the
21 risk of events are much dramatically larger
22 than you had on slide 57. And so I don't

1 want to say, like, this is right or that is
2 right. I'm saying that there's two different
3 ways I think legitimately to look at this
4 data, and one leads to larger estimates of
5 risk of these sedation events over time, both
6 for that calculation, and it would apply also
7 to your projections of what will happen in
8 the first year and how many events you would
9 have in a 5,000-person study.

10 Just that -- you know, there's
11 uncertainty about that and it's related to
12 the model that was picked.

13 DR. ANDERSON: I think taking the
14 calculation a step further, we do have like 390
15 patients who've had at least 35 injections. And
16 so you can get an expected number of patients
17 that'll experience more than one event. And
18 that for the binomial would be -- or the
19 coin-flipping is .1; for the beta-binomial it's
20 1.8. So again, that seemed more of a fit to us.

21 DR. RUDORFER: Dr. Temple?

22 DR. TEMPLE: I'm sure I'm going to

1 embarrass myself with this question, but why
2 can't you just look at the likelihood of one of
3 these events per injection? And then you could
4 do that for Year 1, Year 2, Year 3. You could
5 do it for big people, little people. You could
6 do it for dose. And it wouldn't involve a
7 model, so that the rest of us could understand
8 it. Am I missing something? I mean, doesn't
9 that seem the simplest thing? You want to know
10 on each injection, what's my risk of passing
11 out? That's a simple question.

12 DR. ANDERSON: I think one way that
13 we've done what you've suggested is to use the
14 risk factor analysis and say that for a certain
15 type of patient, once you've incorporated the
16 risks, you're basically left with a binomial.
17 You're left with this coin flipping. You're
18 left with that simple calculation once you've
19 incorporated those risks. Without those risks,
20 we don't think the binomial is as appropriate a
21 model. It would be the beta-binomial.

22 DR. TEMPLE: Okay, but just to be

1 simple-minded, I'd do the whole population
2 first, then I'd break it down into the groups
3 that are probably your factors that you're
4 incorporating into the model, because that
5 allows you to look at big people, little people,
6 first year, second year, third year.

7 Does it change with the number
8 of -- you can ask all of those questions.
9 But if you look at one factor at a time, it's
10 a lot easier to understand than when you sort
11 of do a factor analysis and -- I'm sure there
12 are some people that can understand that, and
13 probably you can, but it's not easy for
14 everybody else. I mean, do you see what I
15 mean? Just what's the -- I mean, it's about,
16 what, .07 -- if you take everybody, it's
17 .07 percent per injection.

18 DR. CORYA: That's right. It's been a
19 very consistent rate over time of .07 percent of
20 injections have resulted in excessive sedation.

21 DR. TEMPLE: And that would be true
22 for Year 1, Year 2, and Year 3. It's about

1 .07 percent. And that would be true for the 200
2 injection, the 300 injection, and the 400
3 injection?

4 Simple questions.

5 DR. CORYA: Yes, it's just that over
6 time, as the patient gets more injections, with
7 each injection --

8 DR. TEMPLE: No, the rate per
9 injection stays the same, or you might think it
10 would stay the same. It doesn't accumulate just
11 because they have had more injections. I want
12 the rate per injection.

13 That's what I think everybody wants
14 to know.

15 DR. CORYA: That is .07, but we
16 don't -- I'm afraid that that is minimizing the
17 risk that will happen to people over time,
18 because the more injections you get, you are
19 more likely to get an event. A single
20 person --

21 DR. TEMPLE: That's okay, I know how
22 to multiply.

1 DR. CORYA: I just want to make sure
2 that we're understanding that the risks can go
3 up over time.

4 DR. TEMPLE: Well, you could also
5 calculate the risk per 10 injections if you
6 wanted to come up with a bigger number that
7 would make people more conscious of what the
8 total risk is. But it would help for comparing
9 things if you did it that way, at least I think
10 so.

11 DR. RUDORFER: Dr. Laughren?

12 DR. LAUGHREN: Well, the question is,
13 does the hazard change over time? Is it a
14 constant hazard or is it an increasing hazard?

15 DR. CORYA: Scott, you mind if I show
16 this graph and we'll see if this answers it? I
17 don't know if this will answer that last
18 question. It's not going to help? I don't
19 know. It sounds like we're going to have to
20 have a statistical discussion over lunch on that
21 one.

22 DR. RUDORFER: Perhaps we'll come back